NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF *p,p′*-DICHLORODIPHENYL SULFONE

(CAS NO. 80-07-9)

IN F344/N RATS AND B6C3F$_1$ MICE

(FEED STUDIES)

NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
Research Triangle Park, NC 27709

September 2001

NTP TR 501

NIH Publication No. 01-4435

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control and Prevention. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

Details about ongoing and completed NTP studies are available at the NTP's World Wide Web site: http://ntp-server.niehs.nih.gov. Abstracts of all NTP Technical Reports and full versions of the most recent reports and other publications are available from the NIEHS' Environmental Health Information Service (EHIS) http://ehis.niehs.nih.gov (800-315-3010 or 919-541-3841). In addition, printed copies of these reports are available from EHIS as supplies last. A listing of all the NTP Technical Reports printed since 1982 appears on the inside back cover.

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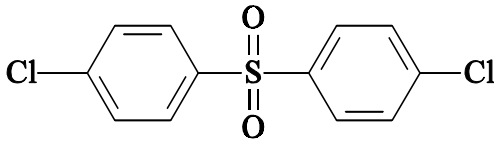
ABSTRACT



_p,p′_-DICHLORODIPHENYL SULFONE

CAS No. 80-07-9

Chemical Formula: $C_{12}H_8Cl_2O_2S$ Molecular Weight: 287.16

Synonyms: Bis (4-chlorophenyl) sulfone; bis (*p*-chlorophenyl) sulfone; 4-chloro-1-(4-chlorophenylsulfonyl) benzene; 4-chlorophenyl sulfone; *p*-chlorophenyl sulfone; 4,4′-dichlorodiphenyl sulfone; 4,4′-dichlorodiphenyl sulphone; di-4-chlorophenyl sulfone; di-*p*-chlorophenyl sulfone; 1,1′-sulfonylbis (4-chlorobenzene)

p,p′-Dichlorodiphenyl sulfone is used as a starting material in the production of polysulfones and polyethersulfones and as a component in reactive dyes in the textile industry; it is also a by-product of pesticide production. *p,p′*-Dichlorodiphenyl sulfone was nominated for study by the National Cancer Institute because of its history of high production and use, the prospect of increased production and use, and the absence of adequate toxicity testing. Male and female F344/N rats and $B6C3F_1$ mice were exposed to *p,p′*-dichlorodiphenyl sulfone (greater than 99% pure) in feed for 14 weeks or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium,* cultured Chinese hamster ovary cells, and mouse bone marrow.

14-WEEK STUDY IN RATS

Groups of 10 male and 10 female F344/N rats were fed diets containing 0, 30, 100, 300, 1,000, or 3,000 ppm *p,p′*-dichlorodiphenyl sulfone (equivalent to average daily doses of approximately 2, 6, 19, 65, or 200 mg *p,p′*-dichlorodiphenyl sulfone/kg body weight) for 14 weeks. All rats survived until the end of the study. Mean body weights of groups exposed to 300 ppm or greater were significantly less than those of the controls. Liver weights of groups exposed to 100 ppm or greater and kidney weights of 1,000 and 3,000 ppm male rats were significantly greater than those of the controls. Centrilobular hepatocyte hypertrophy of the liver was observed in most male rats exposed to 100 ppm or greater and in all female rats exposed to 300 ppm or greater, and the severities were increased in 300 ppm males and 1,000 and 3,000 ppm males and females. The incidences of nephropathy in 1,000 and 3,000 ppm female rats were significantly increased. Dose-related increases in severity of nephropathy were observed in male rats.

14-WEEK STUDY IN MICE

Groups of 10 male and 10 female $B6C3F_1$ mice were fed diets containing 0, 30, 100, 300, 1,000, or 3,000 ppm *p,p′*-dichlorodiphenyl sulfone (equivalent to average daily doses of approximately 3.5, 15, 50, 165, or 480 mg/kg) for 14 weeks. All mice survived until the end of the study. Mean body weights of groups exposed to 300 ppm or greater were significantly less than those of the controls. Liver weights of groups exposed to 300 ppm or greater were significantly increased. Centrilobular hypertrophy of the liver was observed in most males exposed to 100 ppm or greater and in all females exposed to 1,000 or 3,000 ppm, and the severities generally increased with increasing exposure concentration.

2-YEAR STUDY IN RATS

Groups of 50 male and 50 female rats were fed diets containing 0, 10 (males), 30, 100, or 300 (females) ppm *p,p′*-dichlorodiphenyl sulfone for 105 weeks. Dietary concentrations of 10, 30, and 100 ppm resulted in average daily doses of approximately 0.5, 1.5, and 5.0 mg/kg to males. Dietary concentrations of 30, 100, and 300 ppm resulted in average daily doses of approximately 1.6, 5.4, and 17 mg/kg to females. Additional groups of 10 male and 10 female rats were fed the same *p,p′*-dichlorodiphenyl sulfone-containing diets for 18 months and bled for plasma determinations of *p,p′*-dichlorodiphenyl sulfone at approximately 2 weeks and 3, 12, and 18 months.

Survival of all exposed groups of male and female rats was similar to that of the control groups. Mean body weights of 30 and 100 ppm males were generally less than those of the controls during the latter part of the study, and mean body weights of 100 and 300 ppm female rats were less from weeks 30 and 18, respectively. Feed consumption by the exposed groups was similar to that by the controls throughout the study.

The incidences of centrilobular hepatocyte hypertrophy in 100 ppm male and 100 and 300 ppm female rats were significantly greater than those in the controls. The incidences of bile duct hyperplasia and centrilobular degeneration were also significantly increased in 100 and 300 ppm females. No neoplasms were related to chemical exposure.

2-YEAR STUDY IN MICE

Groups of 50 male and 50 female mice were fed diets containing 0, 30, 100, or 300 ppm *p,p′*-dichlorodiphenyl sulfone for 105 to 106 weeks. Dietary concentrations of 30, 100, and 300 ppm delivered average daily doses of approximately 4, 13, and 40 mg/kg to males and approximately 3, 10, and 33 mg/kg to females. Additional groups of 10 male and 10 female mice were fed the same *p,p′*-dichlorodiphenyl sulfone-containing diets for up to 12 months; three mice in each group were bled for plasma determinations of *p,p′*-dichloro-diphenyl sulfone at approximately 2 weeks or 3 or 12 months.

Survival of all exposed groups of male and female mice was similar to that of the control groups. Mean body weights of 300 ppm mice were less than those of the controls throughout most of the study. Feed consumption by the exposed groups was similar to that by the controls throughout the study.

The incidences of centrilobular hepatocyte hypertrophy in all exposed groups of male mice and in 100 and 300 ppm females were significantly greater than those in the controls. The incidence of eosinophilic foci in 300 ppm females was significantly increased. No neoplasms were related to chemical exposure.

PHARMACOKINETICS OF *p,p′*-DICHLORODIPHENYL SULFONE

p,p′-Dichlorodiphenyl sulfone is rapidly absorbed from the gut and metabolized by a saturable process. Although some *p,p′*-dichlorodiphenyl sulfone is eliminated unchanged in feces and urine, most of the elimination is via metabolism. Mathematical modeling of the toxicokinetics supports the view that *p,p′*-dichlorodiphenyl sulfone induces enzymes involved in its metabolism.

GENETIC TOXICOLOGY

p,p′-Dichlorodiphenyl sulfone was not mutagenic in any of several strains of *Salmonella typhimurium*, with or without metabolic activation enzymes (S9). Results of the sister chromatid exchange test in cultured Chinese hamster ovary cells were judged to be negative in the presence of S9 and equivocal in the absence of S9, but no induction of chromosomal aberrations was noted, with or without S9. In contrast to the *in vitro* results, positive results were obtained in an acute *in vivo* mouse bone marrow micronucleus assay with *p,p′*-dichlorodiphenyl sulfone administered by intraperitoneal injection three times over a dose range of 200 to 800 mg/kg.

CONCLUSIONS

Under the conditions of these 2-year feed studies, there was *no evidence of carcinogenic activity** of *p,p′*-dichlorodiphenyl sulfone in male F344/N rats exposed to 10, 30, or 100 ppm or in female F344/N rats exposed to 30, 100, or 300 ppm. There was *no evidence of carcinogenic activity* of *p,p′*-dichlorodiphenyl sulfone in male or female B6C3F_1 mice exposed to 30, 100, or 300 ppm.

Exposure to *p,p′*-dichlorodiphenyl sulfone for 2 years caused increased incidences of nonneoplastic lesions of the liver in male and female rats and mice.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 11. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 13.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of *p,p′*-Dichlorodiphenyl Sulfone

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Concentrations in feed	0, 10, 30, or 100 ppm	0, 30, 100, or 300 ppm	0, 30, 100, or 300 ppm	0, 30, 100, or 300 ppm
Body weights	30 and 100 ppm groups less than control group	100 and 300 ppm groups less than control group	300 ppm group less than control group	300 ppm group less than control group
Survival rates	24/50, 30/50, 20/50, 28/50	36/50, 38/50, 35/50, 35/50	40/50, 45/50, 44/50, 42/50	42/50, 40/50, 43/50, 45/50
Nonneoplastic effects	Liver: centrilobular hypertrophy (0/50, 1/50, 3/50, 16/50)	Liver: centrilobular hypertrophy (0/50, 2/50, 24/50, 38/50); bile duct hyperplasia (5/50, 12/50, 21/50, 32/50); centrilobular degeneration (1/50, 5/50, 10/50, 7/50)	Liver: centrilobular hypertrophy (1/50, 24/50, 43/50, 45/50)	Liver: centrilobular hypertrophy (0/50, 0/50, 9/50, 29/50); eosinophilic focus (2/50, 1/50, 4/50, 14/50)
Neoplastic effects	None	None	None	None
Level of evidence of carcinogenic activity	No evidence	No evidence	No evidence	No evidence
Genetic toxicology				
Salmonella typhimurium gene mutations:	Negative in strains TA97, TA98, TA100, and TA1535 with and without S9			
Sister chromatid exchanges				
Cultured Chinese hamster ovary cells *in vitro*:	Negative with S9; equivocal without S9			
Chromosomal aberrations				
Cultured Chinese hamster ovary cells *in vitro*:	Negative with and without S9			
Micronucleated erythrocytes				
Mouse bone marrow *in vivo*:	Positive when administered by intraperitoneal injection			

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence, including animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results (**clear evidence** and **some evidence**); one category for uncertain findings (**equivocal evidence**); one category for no observable effects (**no evidence**); and one category for experiments that cannot be evaluated because of major flaws (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. Such consideration should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- adequacy of the experimental design and conduct;
- occurrence of common versus uncommon neoplasia;
- progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- combining benign and malignant tumor incidence known or thought to represent stages of progression in the same organ or tissue;
- latency in tumor induction;
- multiplicity in site-specific neoplasia;
- metastases;
- supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- survival-adjusted analyses and false positive or false negative concerns;
- structure-activity correlations; and
- in some cases, genetic toxicology.

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on *p,p′*-dichlorodiphenyl sulfone on 18 May 2000 are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing the NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On 18 May 2000, the draft Technical Report on the toxicology and carcinogenesis studies of *p,p′*-dichlorodiphenyl sulfone received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. R.S. Chhabra, NIEHS, introduced the toxicology and carcinogenesis studies of *p,p′*-dichloro-diphenyl sulfone by discussing the uses of the chemical and the rationale for study, describing the experimental design, reporting on survival and body weight effects, and commenting on compound-related nonneoplastic lesions in male and female rats and mice. The proposed conclusions for the 2-year studies were *no evidence of carcinogenic activity* in male or female F344/N rats or B6C3F$_1$ mice.

Dr. F.M. Parham, NIEHS, said the objective of the toxicokinetic study was to characterize the absorption, distribution, metabolism, and elimination of *p,p′*-dichlorodiphenyl sulfone in rats and mice under the conditions of the 2-year study. Data sources were time-course data for radiolabeled *p,p′*-dichlorodiphenyl sulfone in tissues and exreta after intravenous injection, similar data after single gavage doses, and plasma concentrations of *p,p′*-dichlorodiphenyl sulfone in rats and mice after 2 weeks and 3, 12, and 18 months of exposure in feed. He said the pharmacokinetic model used was similar to the one used in the naphthalene study reported earlier, and that it demonstrated a nonlinear metabolism of *p,p′*-dichlorodiphenyl sulfone by Michaelis-Menten kinetics in the liver. Conclusions from the toxicokinetic studies were that absorption of *p,p′*-dichlorodiphenyl sulfone was very rapid and first-pass liver extraction was very low, while the amount metabolized within the first day was higher. *p,p′*-Dichlorodiphenyl sulfone induced enzymes involved in its metabolism, and elimination half-lives were higher in rats than in mice. Dr. Medinsky said it would be helpful if the NTP could standardize the presentions. Dr. Christopher Portier, NIEHS, agreed and asked for Dr. Medinsky's input to develop a standard format.

Dr. Hecht, a principal reviewer, agreed with the proposed conclusions.

Dr. Bus, the second principal reviewer, agreed with the proposed conclusions. He questioned the designation of a positive response for the mouse micronucleus test, perhaps because of a low control value in the second replicate, and thought *equivocal evidence of carcinogenic activity* might be more appropriate. Dr. Chhabra responded that he discussed this with a genetic toxicologist and they determined that the finding was inconclusive.

Dr. Drinkwater, the third principal reviewer, agreed with the proposed conclusions. He commented that dose-dependent increases in the incidences of eosinophilic foci in the liver of female mice, along with the ability of *p,p′*-dichlorodiphenyl sulfone to cause microsomal enzyme induction and hepatomegaly, are consistent with activity of the chemical as a weak hepatic tumor promoter, and this should be discussed. Dr. Chhabra agreed and said he would clarify this in the Discussion.

Dr. Drinkwater moved that the Technical Report on *p,p′*-dichlorodiphenyl sulfone be accepted with the revisions discussed and with the conclusions as written for male and female rats and mice, *no evidence of carcinogenic activity*. Dr. Cullen seconded the motion, which was accepted unanimously with five votes (Dr. Hecht was absent for the vote).